In the Specification

Please replace the paragraph at page 14, line 26 through page 15, line 24 with the following paragraph:

The CD2BP2 molecule has several unique features that distinguish it from SH3 and WW domain-containing proteins. Although there is some difference in their detailed specificity, SH3 and WW domains both bind to PxxP-containing sequences. Consistent with this specificity, CD2-binding proteins with SH3 domains have been reported, and it has been determined that they mostly bind to the PPLP (SEQ ID NO: 11) sequence (amino acids 302-305 in Fig. 3B), which is an SH3 ligand consensus site (Bell *et al., J. Exp. Med. 183*:169-178 (1997); Gassmann *et al., Eur. J. Immunol. 24*:139-144 (1994)) within the most highly conserved portion of the CD2 tail segment. In contrast, CD2BP2 binds to a site containing the two tandem PPPGHR (SEQ ID NO: 10) motifs but not to the SH3 ligand consensus sites (Fig. 3B). Moreover, unlike SH3 domains whose ligands require only eight residues for binding (Ren *et al., Science 259*:1157-1161 (1993); Musacchio *et al., Prog. Biophys. Mol. Biol. 61*:283-297 (1994)), CD2BP2 requires a 21-residue segment. It is believed that this CD2BP2 binding segment transiently assumes a configuration necessary for interaction, perhaps regulated by divalent cations. Conservation of the dibasic residues within the two tandem motifs, including the histidine in human, mouse, rat, and horse CD2, is noteworthy. It has previously been shown that the PPPGHR (SEQ ID NO: 10)-containing region of the CD2 tail is essential for CD2 ectodomain-stimulated IL-2 production (Chang *et al., J. Exp. Med. 169*:2073-2083 (1989); Chang *et al., J. Exp. Med. 172*:351-355 (1990)). Although the mechanism by which the tandem PPPGHR (SEQ ID NO: 10) sequences trigger IL-2 gene activation on CD2 clustering is still unclear, it is possible that this region is needed for the proper orientation and/or function of the downstream SH3 ligand binding motif. Consistent with this notion, replacement of the dibasic HR residues of the PPPGHR (SEQ ID NO: 10) segment with DE residues weakens not only the binding of CD2BP2 to this region but also that of the SH3 domain of $p59^{fyn}$ to the downstream SH3 consensus site. Thus, it is believed that CD2BP2 may play a biologic role in coordinating the binding of other interactors to the more C-terminal region of the CD2 tail.

Please replace the paragraph at page 15, line 24 through page 16, line 17 with the following paragraph:

SH3 domains are made up of 5-6 antiparallel β-strands forming a compact, barrel-like structure. As shown by analysis of complexes of SH3 domains and their ligands, the ligand for a given SH3 domain forms a left-handed polyproline-type II helix whose interactions with the SH3 domain are mediated primarily by hydrophobic residues within the binding site (Ren *et al., Science 259*:1157-1161 (1993); Musacchio *et al., Prog. Biophys. Mol. Biol. 61*:283-297 (1994)). WW domains form a three-stranded antiparallel β-strand with one of the two conserved tryptophan residues crucially involved in the interaction with the proline-rich ligand (Macias *et al., Nature 382*:646-649 (1996)). The *in vivo* binding assays described herein show that a number of aromatic residues of CD2BP2 probably are involved directly in the interaction with the proline-rich sequence motif of the CD2 cytoplasmic domain. However, structure-prediction methods and initial Nuclear Overhausen Effect (NOE) analysis indicate the presence of a central α-helix within the binding domain of CD2BP2 (residues 301-311). This helix is predicted to reside within the conserved 17-amino acid sequence shown herein to be necessary for the binding of the proline-rich ligand. It therefore appears that the binding domain of CD2BP2 defines a class of proline-rich recognition domains. In this fold, an α-helical rather than a β-strand structure displays those aromatic and hydrophobic residues necessary for the binding to the proline-rich ligand. Given that the CD2BP2 protein involved in binding to the PPPGHR (SEQ ID NO: 10) motif is expressed in different tissues, and that there is conservation of the GP[Y/F]xxxx[M/V]xxWxxxGYF (SEQ ID NO: 9) sequence in other unrelated proteins derived from different species, it is likely that this interaction is not restricted to lymphocytes, but rather represents a basis for protein-protein interaction.

Please replace the paragraph at page 19, line 4 through page 20, line 2 with the following paragraph:

Close inspection of the ligand binding site of the CD2BP2 GYF domain shows it to display a slightly bent, relatively smooth surface (Fig. 8A). A proline-rich ligand might be anticipated to bind along the axis defined by the α-helical residues of the binding site. Since four residues of the sequence PXXP (Pawson, *Nature 373*:573-580 (1995)) are able to adopt a proline-helical conformation, the PPPP (amino acids 1-4 or 15-18 of SEQ ID NO: 22) sequence of the PPPPGHR (amino acids 1-7 or 15-21 of SEQ ID NO: 22) repeat could assume such a conformation as well. Fig. 8B shows the surface area occupied by the conserved residues of the homology region of the GYF domain. Except for Y6, which is largely buried in the core of the protein, this area forms a subset of the contiguous surface of the whole binding site of the CD2BP2 GYF domain (Fig. 8A and 8B in comparison). We suggest that the conserved hydrophobic patch defines the major binding surface interacting with proline-rich ligands. This is likely to be the case for CD2BP2 as well as for all the other proteins containing the homology region of the CD2BP2 GYF domain (Fig. 6). We speculate furthermore that, since only 6-8 residues can be placed along this hydrophobic patch, one of the two proline-rich repeats in the CD2 tail is primarily responsible for the binding to the conserved residues of the homology region. In agreement with this hypothesis, the arrangement of two tandem PPPPGHR (amino acids 1-7 or 15-21 of SEQ ID NO: 22) segments seems to be a peculiarity of the CD2 cytoplasmic domain, since a Ψ-BLAST sequence search (Altschul, *et al., Nucleic Acids Res. 25*:3389-3402 (1997)) revealed no significant homology to the PPPPGHRSQAPSHRPPPPGHR (SEQ ID NO: 22) sequence found in CD2. In addition, the distribution of charged residues within the homology region is different for each of the proteins compared in Fig. 6, implying that charged interactions might not be a conserved feature of the homology region containing proteins. In the case of the CD2BP2 GYF domain, however, E31 and D36 are part of the NMR mapped binding site and an number of additional negatively charged residues are located at the edge of the binding surface (Fig. 8C). No positive charge is present on this surface, suggesting that only acidic residues confer specificity to the interaction with the CD2 cytoplasmic domain, probably by interacting with the HR residues of the PPPPGHR (amino acids 1-7 or 15-21 of SEQ ID NO: 22) sequence.

Please replace the paragraph at page 20, line 3 through page 21, line 2 with the following paragraph:

The fold of the GYF domain is unrelated to the structures of SH3 (Musacchio, *et al., Nature 359*:851-855 (1992); Yu, *et al., Science 258*:1665-1668 (1992)) or WW (Macias, *et al., Nature 382*:646-649 (1996)) domains, which display the side-chains for the interaction with the proline-rich ligand by means of β-strands and β-strand connecting loops. Nonetheless, there are some features shared between all three protein modules. For example, conserved hydrophobic residues line up to create a contiguous surface stretch. These residues define the axis for the binding of the proline-rich ligand in the case of SH3 and WW domains and we suggest this to be the case for the GYF domain as well. Second, glutamine or asparagine side-chains within SH3 and WW domains contribute to the interaction with the respective peptides by the potential formation of hydrogen bonds (Macias, *et al., Nature 382*:646-649 (1996); Musacchio, *et al., Prog. Biophys. Mol. Biol.* 61:283-297 (1994)). In the case of the GYF domain the side-chain amide protons of Q48 become largely shifted upon addition of the proline-rich ligand (Nishizawa, *et al., Proc. Natl. Acad. Sci. USA 95:*14897-14902 (1998)), indicating a direct interaction with the ligand. Third, a specificity pocket within SH3 and WW domains interacts with non-proline residues of the ligand, restricting the promiscuity of these domains. The surface properties and charge distribution of the GYF domain binding site also argues for the necessity of non-proline residues to be present in the ligand for an optimal interaction. Residues E31 and Y33 extrude significantly from the surface, creating a wall at the C-terminal end of the α-helix. In order to interact with residues of the α-helix as well as the site defined by W8 and its spatially adjacent residues, one or more non-proline residues probably have to allow the ligand to bent around these extruding side-chains. The presence of a glycine residue within the PPPPGHR (amino acids 1-7 or 15-21 of SEQ ID NO: 22)-recognition motifs could provide this conformational flexibility within the ligand. Finally, the N– and C-terminus of all three domains are close in space. This facilitates the ability of SH3 and WW domains to function as universal protein-protein interaction modules present in many

proteins involved in signal transduction. A similar adapter function might be anticipated for the GYF domain.

Please replace the paragraph at page 27, lines 14 through 27 with the following paragraph:

The determination of percent identity between two sequences can be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin *et al.*, *Proc. Natl. Acad. Sci. USA*, *90*:5873-5877 (1993). Such an algorithm is incorporated into the NBLAST program which can be used to identify sequences having the desired identity to nucleotide sequences of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, *Nucleic Acids Res, 25*:3389-3402 (1997). When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., NBLAST) can be used. In one embodiment, parameters for sequence comparison can be set at W=12. Parameters can also be varied (e.g., W=5 or W=20). The value "W" determines how many continuous nucleotides must be identical for the program to identify two sequences as containing regions of identity.

Amendments to the specification are indicated in the attached "Marked Up Version of Amendments" (pages i - v).

In the Claims

Please amend Claims 7-13, 22, and 44-46.

7. (Amended) An isolated nucleic acid molecule which encodes a protein comprising SEQ ID NO: 2, or a fragment of said protein having biological activity of polypeptides of SEQ ID NO: 3 or SEQ ID NO: 9, or the complement of said nucleic acid molecule.

8. (Amended) An isolated nucleic acid molecule possessing sequence identity of at least 80% with the nucleic acid molecule of Claim 7, wherein said nucleic acid molecule encodes a fragment of a protein of SEQ ID NO: 2 and wherein said fragment has biological activity of polypeptides of SEQ ID NO: 3 or SEQ ID NO: 9, or the complement of said nucleic acid molecule.

9. (Amended) An isolated nucleic acid molecule of Claim 7, wherein said nucleic acid molecule has the same nucleotide sequence as an endogenous gene encoding a protein of SEQ ID NO: 2.

10. (Amended) An isolated nucleic acid molecule of Claim 7, wherein said nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:1.

11. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 3.

12. (Amended) An isolated nucleic acid molecule consisting of a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 9.

13. (Amended) An isolated nucleic acid molecule consisting of a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 10.

22. (Amended) A method for preparing a protein of SEQ ID NO: 2, or a fragment thereof, wherein said fragment has biological activity of polypeptides of SEQ ID NO: 3 or SEQ ID NO: 9, comprising culturing the recombinant host cell of Claim 18.

44. (Amended) An isolated recombinant nucleic acid molecule comprising a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 3, wherein said nucleotide sequence is heterologous.

45. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 9, wherein said nucleotide sequence is heterologous.

46. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 10, wherein said nucleotide sequence is heterologous.

Amendments to the claims are indicated in the attached "Marked Up Version of Amendments" (pages vi - vii).

Please add new Claims 54-61.

54. (New) An isolated nucleic acid molecule consisting of a nucleotide sequence encoding the amino acids 1 through 7 of SEQ ID NO: 22.

55. (New) An isolated nucleic acid molecule which encodes a fragment of SEQ ID NO: 2, comprising a polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 9, or the complement of said nucleic acid molecule.

56. (New) A nucleic acid construct comprising the isolated nucleic acid molecule of Claim 55 operably linked to a regulatory sequence.

57. (New) A recombinant host cell comprising the nucleic acid construct of Claim 55.

58. (New) A method for preparing a fragment of SEQ ID NO: 2, wherein said fragment comprises a polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 9, said method comprising a step of culturing a recombinant host cell of Claim 55.

59. (New) An isolated nucleic acid molecule of Claim 7, wherein biological activity is binding to a CD2 molecule.

60. (New) An isolated nucleic acid molecule of Claim 8, wherein biological activity is binding to a CD2 molecule.

61. (New) A method of Claim 22, wherein biological activity is binding to a CD2 molecule.

REMARKS

Amendments to the Specification

The specification has been amended to correct formal matters as requested by the Examiner, particularly to insert missing SEQ ID NOS: and to delete a hyperlink. These amendments introduce no new matter.

Claim Amendments

Claims 7-13 have been amended to insert an indefinite article as requested by the Examiner. This amendment introduces no new matter.

Claims 7-9 have been amended to recite "protein of SEQ ID NO: 2" and to delete references to a "derivative". Support for this amendment is found throughout specification, for example, on page 10, line 8 and on page 60, line 6.

Claims 7 and 8 have been amended to recite "biological activity of polypeptides of SEQ ID NO: 3 or SEQ ID NO: 9". Support is found, for example, on page 59, lines 9-16 and page 28, lines 10-13 and page 30, line 15.

Claim 8 has been amended to recite "an isolated nucleic acid molecule possessing sequence identity of at least 80% with the nucleic acid molecule of Claim 7". Support and definitions are found, for example, page 27, lines 1-5 and 14-27.

Claim 9 has been amended to recite "an endogenous gene". Support is found, for example, on page 3, line 3.